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(54) **Thiazolidine derivatives, their production and use.**

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EP-A- 0 177 353

Chem. Pharm. Bull. 30 (1982), pp. 3563,3580,3886

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D scription

This invention relates to novel thiazolidinedione derivatives having blood sugar and lipid low ring activity, methods of producing the same and antidiabetic agents containing the same.

Various biguanide type compounds and sulfonylurea type compounds have so far been used as antidiabetic agents. However, biguanides are rather obsolete nowadays because they induce lactic acidosis. Sulfonylureas, on the other hand, have potent blood sugar lowering activity but frequently cause severe hypoglycemia, so that much care is necessary in using them. Accordingly, the appearance of novel type antidiabetics free of these drawbacks has been waited for. Meanwhile, Japanese Patent Publications Kokai No. 22636/80 and Kokai No. 64586/80, Chemical & Pharmaceutical Bulletin, vol. 30, p. 3563 (1982), ibid., vol. 30, p. 3580 (1982) and ibid., vol. 32, p. 2257 (1984) and EP-A-0008203 describe that various thiazolidinedione derivatives exhibit blood sugar and lipid lowering activity,Antidiabetic activity of ciglitazone was also reported in Diabetes, 32, P.804 (1983). None of them, however, has not come into practical use as an antidiabetic agent mainly because they are (1) weak in effect and/or (2) high in toxicity.

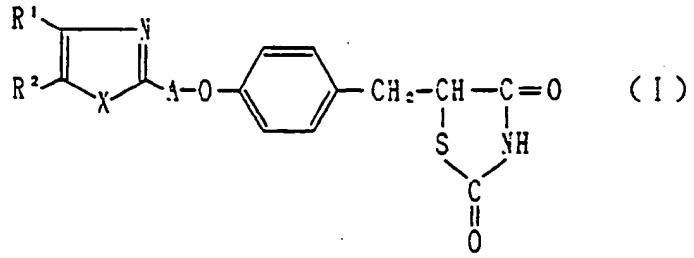
Other thiazolidenedione derivatives of therapeutic value for diabetes and hyperlipemia are disclosed in EP-A-0 177 353.

The present inventors synthesized and evaluated various compounds not specifically described in the above-cited patent publications and, as a result, compounds having potent pharmacological activity with low toxicity were found.

It is an object of the invention to provide those compounds which have a wide safety margin between the pharmacologically effective dose and the dose at which toxicity and/or adverse effects may appear and therefore can be put to practical use as antidiabetics.

The present invention thus provides:

(1) Thiazolidinedione derivatives of the general formula:



(I)

wherein

X is an oxygen or sulfur atom,

R^1 and R^2 each independently is

a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms,

a saturated alicyclic hydrocarbon residue containing 3 to 7 carbon atoms,

an unsaturated alicyclic hydrocarbon residue containing 5 to 7 carbon atoms,

a group resulting from bonding the above-mentioned alicyclic hydrocarbon residue to the above-mentioned aliphatic hydrocarbon residue and containing 4 to 9 carbon atoms,

a phenylalkyl group containing 7 to 9 carbon atoms,

a naphthylalkyl group containing 11 to 13 carbon atoms, phenyl or naphthyl;

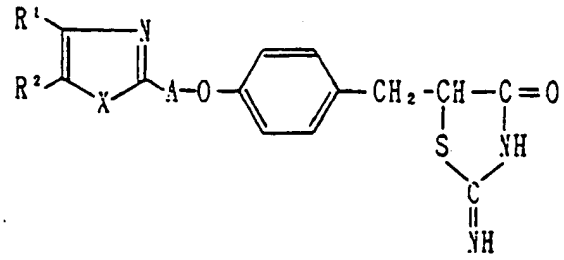
i) R^1 and R^2 each being unsubstituted or substituted by one to three lower alkyl groups containing 1 to 3 carbon atoms when R^1 and R^2 each is an alicyclic hydrocarbon or contains an alicyclic hydrocarbon, or

ii) R^1 and R^2 each being unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms when R^1 and R^2 each is phenyl or naphthyl or contains phenyl or napnthyl,

or

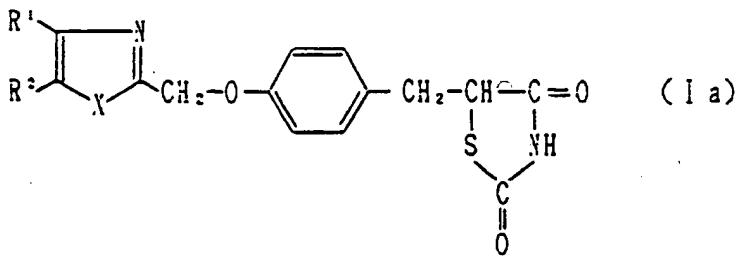
R^1 and R^2 are combined together to form a saturated or unsaturated divalent chain hydrocarbon residue containing 3 to 5 carbon atoms, which is unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms,

and
A is a lower alkyl n group having 1 to 3 carbon atoms, or a salt thereof.
(2) Pharmaceutical compositions suitable for the therapy of a mammal suffering from diabetes and/or hyperlipemia, which contain as the effectiv component a thiazolidinedione d rivative of th general formula (I) or a pharmacologially acceptable salt thereof.
(3) A method of producing thiazolidinedione derivatives of the general formula (I) and salts thereof which comprises hydrolyzing a compound of the general formula:



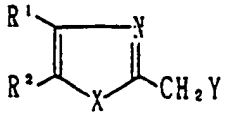
(II)

wherein the symbols are as defined above, or a salt thereof; and
(4) A method of producing thiazolidinedione derivatives of the general formula:



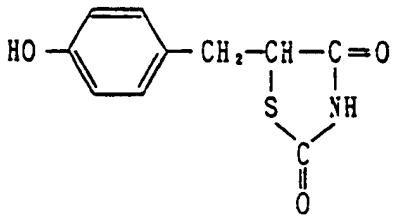
(Ia)

wherein the symbols are as defined above, and salts thereof, which comprises reacting a compound of the general formula:



(III)

wherein R^1, R^2 and X are as defined above and Y is a halogen atom, with a compound of the formula:



(IV)

The hydrocarbon residue represented by R^1 and/or R^2 in the above general formulas (I), (Ia), (II) and (III) is an aliphatic hydrocarbon residue, an alicyclic hydrocarbon residue, an alicyclic-aliphatic hydrocarbon residue, an aromatic-aliphatic hydrocarbon residue or an aromatic hydrocarbon residue. Said aliphatic hydrocarbon residue is saturated aliphatic hydrocarbon residues containing 1-8 carbon atoms, (e.g. methyl,

ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl and octyl), preferably 1-4 carbon atoms; said alicyclic hydrocarbon residue is saturated alicyclic hydrocarbon residues containing 3-7, preferably 5-6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and unsaturated alicyclic hydrocarbon residues containing 5-7 carbon atoms, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl and 2-cycloheptenyl; said alicyclic-aliphatic hydrocarbon residue is groups resulting from bonding the above-mentioned alicyclic hydrocarbon residues to the above-mentioned aliphatic hydrocarbon residues and containing 4-9 carbon atoms, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, cycloheptylmethyl and cycloheptylethyl; said aromatic-aliphatic hydrocarbon residue is phenylalkyl groups containing 7-9 carbon atoms, such as benzyl, phenethyl, 1-phenylethyl and phenylpropyl, and naphthylalkyl groups containing 11-13 carbon atoms, such as α-naphthylmethyl, α-naphthylethyl and β-naphthylethyl; and said aromatic hydrocarbon residue is phenyl and naphthyl (α-naphthyl, β-naphthyl). By saying that R^1 and R^2 jointly, together with the oxazole or thiazole ring, form a condensed ring, it is precisely meant that R^1 and R^2, together with the thiazole or oxazole ring carbon atoms to which they are attaching, form a ring. Thus, it is meant that R^1 and R^2 are combined together to form a saturated or unsaturated divalent chain hydrocarbon residue containing 3-5 carbon atoms. Examples of said chain hydrocarbon residue are $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH=CHCH_2-$, $-CH=CH-CH=CH-$, $-CH=CH-CH=CH-CH_2-$ and $-CH=CH-CH_2CH_2CH_2-$.

The hydrocarbon residue represented by R^1 and/or R^2 may have at least one substituent in any position thereof. When R^1 and/or R^2 contains an alicyclic group, R^1 and/or R^2 may have, on the ring thereof, 1-3 lower alkyl groups containing 1-3 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl). When R^1 and/or R^2 contains an aromatic hydrocarbon residue or when R^1 and R^2 combinedly form a condensed ring, the ring may be substituted with 1-4 substituents, which may be the same or different. Said substituents are halogen (fluorine, chlorine, iodine), hydroxy, cyano, trifluoromethyl, lower alkoxy (e.g. one containing 1-4 carbon atoms, such as methoxy, ethoxy, propoxy or butoxy), lower alkyl (e.g. one containing 1-4 carbon atoms, such as methyl, ethyl, propyl, isopropyl or butyl) and lower alkylthio (e.g. one containing 1-3 carbon atoms, such as methylthio, ethylthio, propylthio or isopropylthio).

A lower alkylene group represented by A is a straight or branched chain having 1 to 3 carbon atoms and includes methylene, ethylene, propylene and trimethylene.

The halogen represented by Y in formula (III) includes chlorine, bromine and iodine.

Compounds of the general formula (I) can form salts with bases since they have an acidic nitrogen atom in their thiazolidine ring. Such salts include, among others, pharmacologically acceptable salts such as sodium, potassium, magnesium and calcium salts.

The compounds (I) and salts thereof according to the invention exhibit excellent blood sugar and blood lipid lowering activities in mammals (e.g mouse, rat, dog, cat, monkey, horse, human) and are low in acute toxicity as well as in subacute toxicity. Therefore, the thiazolidinedione derivatives (I) and salts thereof are useful in the treatment of hyperlipidemia and/or diabetes and complications resulting therefrom. They are generally administered orally in the form of tablets, capsules, powders or granules, for instance. In some instances, they may be administered parenterally in the form of injections, suppositories or pellets, among others. In using them as therapeutic agents for diabetes or hyperlipidemia, they can be administered generally in an oral daily dose of 0.01-10 mg/kg or a parenteral daily dose of 0.005-10 mg/kg. Desirably, they are administered in such dose every day or intermittently 2-4 times a week.

The compounds of general formula (I) or salts thereof can be produced by hydrolyzing the compounds of general formula (II) or salts thereof. This hydrolysis reaction is generally carried out in an appropriate solvent in the presence of water and a mineral acid. Examples of the solvent which are generally used are alkanols (e.g. methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, 2-methoxyethanol), dimethyl sulfoxide, sulfolane, dioxane and dimethoxyethane. The mineral acid is, for example, hydrochloric acid, hydrobromic acid or sulfuric acid and is used in an amount of 0.1-10 moles, preferably 0.2-3 moles, per mole of the compound of general formula (II). Water is used generally in large molar excess relative to the compound of general formula (II). This reaction is generally carried out with warming or heating and the reaction temperature is generally 60-150°C. The heating time is g nerally several hours to ten and odd hours.

Those compounds of general formula (I) wherein A is methylene and salts thereof, namely the compounds of general formula (Ia) and salts thereof [hereinaft r collectively referred to as "compounds (Ia)-"], can be obtained by reacting a compound of general formula (III) with a compound of general formula (IV) or a salt thereof [hereinafter collectively referred to as "compound (IV)"]. The reaction of the compound of general formula (III) and the compound (IV) is generally carried out in the presence of an appropriate

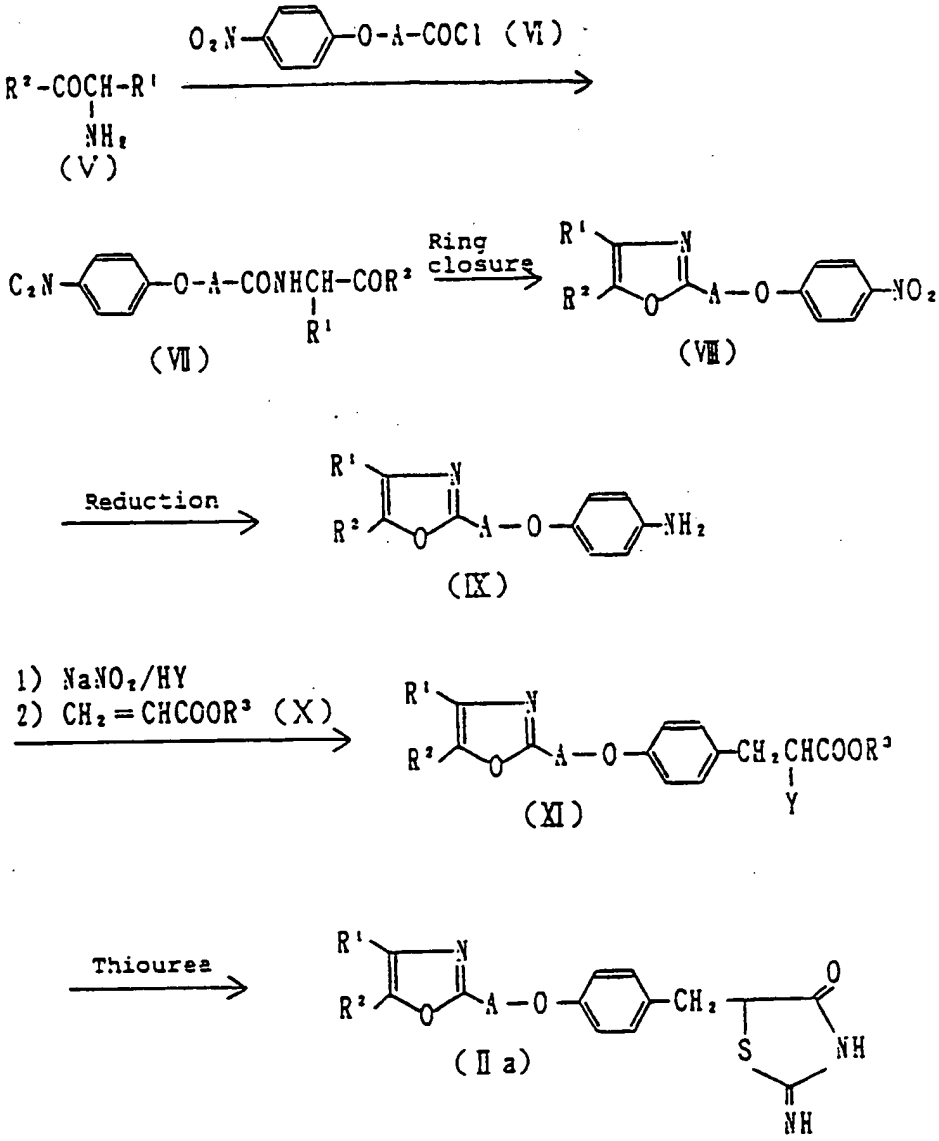
solvent and an appropriate base and this reaction gives th compounds (Ia).

Such solvent includes, among others, dimethylformamide, dimethyl sulfoxide, sulfolane, tetrahydrofuran and dimethoxyethane. Examples of said base are sodium hydride, potassium hydride, sodium amid , sodium alkoxide (e.g. sodium methoxide, sodium ethoxide), potassium alkoxide (e.g. potassium t-butoxide) and potassium carbonate. This reaction is preferably carried out by first allowing formation of a dianion by bringing such base into contact with the compound (IV) in a molar ratio of 2:1 and thereafter adding the compound of general formula (III) in an amount of 1 mole per mole of compound (IV). This condensation reaction is carried out generally at 0°-120°C, preferably 20°-100°C, and the reaction time is generally 0.5-5 hours.

The thus-produced thiazolidinedione derivatives (I) and salts thereof can be isolated and purified by known separation/purification techniques such as, for example, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer and chromatography.

The starting compounds (II) can be produced, for example, by the following methods:

1) The process illustrated below gives those compounds of general formula (I) wherein X is an oxygen atom, namely the compounds of general formula (IIa), and salts thereof [hereinafter collectively referred to as "compounds (IIa)].



[In the above formulas, R^1, R^2 and A are as defined above and R^3 is hydrogen or a lower alkyl group.]

The r action for deriving the compound (VII) from the compound (V) is carried out in the manner of condensation of the compound (V) with the compound (VI) in the presence of a deacidifying agent (e.g. potassium carbonate, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium hydroxide, potassium hydroxide, triethylamine). This reaction can be conducted in a solvent, such as dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, ethyl ether, ethyl acetate, chloroform or dichloromethane, or a mixed solvent prepared by adding water to such solvent as necessary, at -10° C to 50° C.

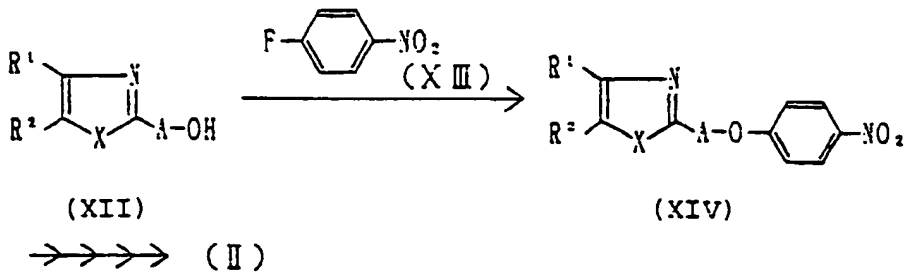
The compound (VII) is then subjected to ring closure, whereby the compound (VIII) can be derived. This reaction is carried out generally in the presence of a dehydrating agent. Known dehydrating agents, such as phosphorus oxychloride, thionyl chloride, phosphorus pentoxide, polyphosphoric acid, polyphosphoric acid esters, acetic anhydride and sulfuric acid, and mixtures of these, may suitably be used. Although the reaction conditions may vary depending on the dehydrating agent employed, this reaction can be effected generally in an inert solvent (e.g. benzene, toluene, xylene, dichloromethane, chloroform) at about 30°-140° C, or in an excess of the dehydrating agent, which serves also as a solvent, within said temperature range. The dehydrating agent is used in an amount of 1-30 moles per mole of compound (VII).

The reaction for deriving the compound (IX) from the compound (VIII) can be readily carried out in the manner of a conventional catalytic reduction using palladium-on-carbon as catalyst or a conventional reduction using zinc or iron in combination with acetic acid. The compound (IX) may be isolated in pure form or may be subjected to the next reaction step without isolation or purification.

The reaction for deriving the compound (XI) from the compound (IX) is carried out in the manner of the so-called Meerwein arylation. Thus, the compound (IX) is diazotized in the presence of a hydrohalogenic acid (HY) and then reacted with acrylic acid or an ester thereof (X) in the presence of a copper catalyst (e.g. cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide). The compound (IX) may be purified, for example by chromatography or may be submitted to the next reaction step without isolation and purification.

Reaction of the compound (XI) with thiourea then gives (IIa). This reaction is carried out generally in a solvent such as an alcohol (e.g. methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, 2-methoxyethanol), dimethylformamide, dimethyl sulfoxide or sulfolane. The reaction temperature is generally 20°-180° C, preferably 60°-150° C. Thiourea is used in an amount of 1-2 moles per mole of compound (XI). In this reaction, a hydrogen halide is formed as a byproduct with the progress of the reaction, whereby the hydrohalogenic acid salt of compound (IIa) is formed. In this case, the reaction may be carried out in the presence of sodium acetate, potassium acetate or the like so that the hydrogen halide can be captured thereby and (IIa) can be produced in the free form. Such acid acceptor is used generally in an amount of 1-1.5 moles per mole of compound (XI). Such reaction gives the compound (IIa), which may be isolated as desired or may be submitted directly to the next hydrolysis step without isolation thereof.

2) The compounds (II) can also be produced by the following process:



In the formulas, the symbols are as defined above.

In the above process, the compound (XII) is reacted with the compound (XIII) and thereafter, in the same manner as in the case of (VIII) in the process 1) described above, the resulting compound (XIV) is reduced, diazotized and subjected to the Meerwein arylation reaction. Further reaction of the arylation product with thiourea gives (II). The reaction of (XII) with (XIII) can be carried out in a solvent, such as dimethylformamide or tetrahydrofuran, in the presenc of, for example, sodium hydride.

Furthermore, the starting compound (IV) required in practising the present invention can be

synthesized by the method described in Chemical & Pharmac utical Bulletin, vol. 30, p. 3563 (1982).

[Examples]

Example 1

A mixture of 2-imino-5-{(4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]benzyl}-4-thiazolidinone (5.5 g), ethanol (100 ml) and 2 N HCl (60 ml) was heated under reflux for 6 hours and then poured into water and extracted with chloroform. The chloroform layer was washed with water and dried ($MgSO_4$). The solvent was distilled off to give 5-{4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy}-2,4-thiazolidinedione (2.8 g, 50.9%). Recrystallization from ethyl acetate gave colorless prisms. M.p. 168-169° C.

Elemental analysis

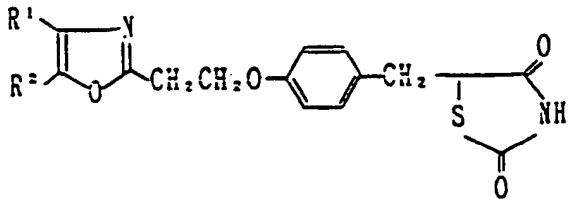
Calcd. for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.93; N, 6.86

Found: C, 64.90; H, 5.05; N, 6.82

Examples 2-3

In the same manner as Example 1, the compounds listed in Table 1 were obtained.

Table 1



Example NO.	R^1	R^2	M.p. (°C)	Recrystallization solvent	Yield (%)
2	$(CH_3)_2CHCH_2-$	CH_3	123-124	Ethyl acetate-hexane	88.0
3		CH_3	175-176	Ethanol-dichloromethane	48.2

Example 4

A mixture of 2-imino-5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-4-thiazolidinone (7.6 g), 1 N H_2SO_4 (70 ml) and dioxane (70 ml) was stirred at 80° C for 24 hours and then concentrated. Th residue was neutralized with potassium carboante and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off and the oily residue was subjected to column chromatography using silica gel (120 g).
Elution with chloroform-methanol (49:1, v/v) gave 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione as an oil (7.06 g, 92.7%).

IR(Neat)cm^{-1}: 1755, 1700
NMR δ ppm in $CDCl_3$: 2.48(3H,s), 3.02(1H,d.d,J = 14 and 9), 3.21(2H,t,J = 7), 3.41(1H,d.d,J = 14 and 4), 4.35(2H,t,J = 7), 4.41(1H,d.d,J = 9 and 4), 6.84(2H,d,J = 9), 7.11(2H,d,J = 9), 7.2–7.75(5H, m), 9.30-(1H,broad)

The above-obtained oily substance (7.0 g) was dissolved in methanol (50 ml), and 5 N NaOMe (MeOH solution, 3.77 ml) was added to the solution. The mixture was stirred at room temperature for 10 minutes and concentrated and, then, the residue was treated with ether to give sodium salt of 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione (5.8 g, 78.6%). Recrystallization from methanolether gave colorless prisms. M.p. 261-262° C (decomposition).

Elemental analysis

Calcd. for $C_{22}H_{19}N_2O_4SNa$: C, 61.39; H, 4.45; N, 6.51

Found : C, 61.56; H, 4.56; N, 6.64

Example 5

The procedure of Example 4 was followed to give sodium salt of 5-{4-[2-(5-ethyl-4-phenyl-2-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione in 76.9% yield. Recrystallization from ethanol gave colorless prisms. M.p. 248-250° C (decomposition).

Elemental analysis

Calcd. for $C_{23}H_{21}N_2O_4SNa$: C, 62.15; H, 4.76; N, 6.30

Found : C, 61.76; H, 4.66; N, 6.40

Reference Example A

Sodium hydride (60% in oil, 1.2 g) was added to a solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (3.4 g) in DMF (30 ml), and the mixture was stirred at room temperature for 30 minutes, followed by dropwise addition of a solution of 2-chloromethyl-4-phenylthiazole (4.4 g) in DMF (20 ml) at room temperature. The mixture was stirred at room temperature for 1 hour and at 60° C for 1 hour, poured into water, neutralized with acetic acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off and the oily residue was subjected to column chromatography using silica gel (100 g). Elution with benzene-acetone (25:1, v/v) gave 5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]-2,4-thiazolidinedione (2.9 g, 49.2%). Recrystallization from ethanol gave light-yellow crystals. M.p. 164-165° C.

Elemental analysis

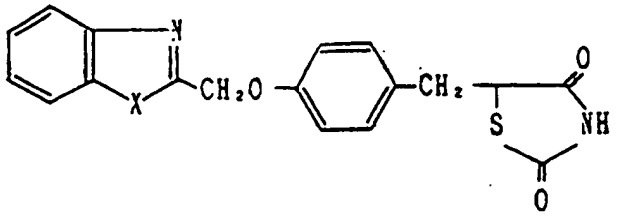
Calcd. for $C_{20}H_{16}N_2O_3S_2$: C, 60.59; H, 4.07; N, 7.07

Found : C, 60.67; H, 4.03; N, 7.14

Examples 6-7

The procedure of Reference Example A was repeated to give the compounds listed in Table 2.

Table 2



Example No.	X	M.P. (°C)	Recrystallization solvent	Yield (%)
6	O	188-189	Dichloromethane-methanol	32.5
7	S	184-185	Dichloromethane-methanol	35.3

Example 8

Production of tablets

a) (1)	Sodium salt of 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione	30 g
(2)	Lactose	50 g
(3)	Corn starch	15 g
(4)	Carboxymethylcellulose calcium	44 g
(5)	Magnesium stearate	1 g
	1,000 tablets	140 g

A mixture of the indicated quantities of (1), (2) and (3), 30 g of (4) and an adequate quantity of water is kneaded, then dried under vacuum, and granulated. The granular composition obtained is mixed with 14 g of (4) and 1 g of (5) and the resulting mixture is tableted on a tableting machine to give 1,000 tablets each containing 30 mg of (1).

Reference Example 1

A mixture of 3-(4-nitrophenoxy)propionic acid (10.5 g), thionyl chloride (11.9 g), N,N-dimethylformamide (0.3 g) and toluene (100 ml) was stirred at 90° C for 1 hour,then concentrated under reduced pressure, and the oily residue was dissolved in ethyl acetate (30 ml). The solution was added dropwise to a mixture of 3-amino-5-methyl-2-h xanone hydrochloride (8.3 g), sodium carbonate (10.6 g), water (200 ml) and ethyl ac tate (100 ml) at room temperature. The mixture was stirred at room temperature for 1 hour and the ethyl acetate layer was separated. The ethyl ac tate layer was washed with water and dried ($MgSO_4$). The solvent was distilled off to give 3-[3-(4-nitroph noxy)propionylamino]-5-methyl-2-hexanone (11.5 g, 71.4%). Recrystallization from thyl acetate-hexane gave colorless prisms. M.p. 101-102° C.

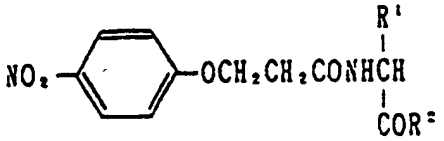
Elemental analysis

Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69

Found : C, 59.67; H, 6.79; N, 8.61

In the same manner as above, there were obtained the compounds listed in Table 3.

Table 3



R^1	R^2	M.P. (°C)	Recrystallization solvent	Yield (%)
CH_3		134-135	Ethyl acetate-hexane	75.5
	CH_3	131-132	Ethyl acetate	79.6
	CH_3	143-144	Ethyl acetate-hexane	63.2
	C_2H_5	132-133	Ethyl acetate	76.2

Reference Example 2

A mixture of 3-[3-(4-nitrophenoxy)propionylamino]-5-methyl-2-hexanone(11.0 g), phosphorus oxychloride (6.3 g) and toluene (100 ml) was stirred under reflux for 1 hour. After cooling, the mixture was poured into ethyl acetate (200 ml), washed with saturated aqueous sodium hydrogen carbonate and water in that order and dried ($MgSO_4$). The solvent was then distilled off and the oily residue was subjected to column chromatography using silica gel (150 g), whereby 4-isobutyl-5-methyl-2-[2-(4-nitrophenoxy)ethyl]oxazole (8.1 g, 78.6%) was recovered from an ethyl acetate-hexane (1:4, v/v) eluate fraction. Recrystallization from ether-hexane gave colorless needles. M.p. 45-46 °C.

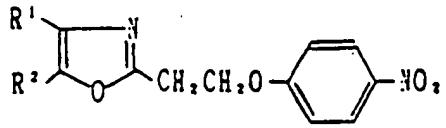
Elemental analysis

Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20

Found : C, 63.14; H, 6.44; N, 9.27

In the same manner as above, there were obtained the following compounds listed in Table 4.

Table 4



R^1	R^2	M. P. (°C)	Recrystallization solvent	Yield (%)
CH_3		117-118	Ethyl acetate-hexane	89.0
	C_2H_5	72- 73	Ether-hexane	89.5
	CH_3	91- 92	Ether-hexane	81.7
	CH_3	88- 89	Ether-hexane	85.3

Reference Example 3

A solution of 4-methyl-2-[2-(4-nitrophenoxy)ethyl]-5-phenyloxazole (12.5 g) in methanol (150 ml) was subjected to catalytic reduction in the presence of 5% Pd-C (wet, 3.0 g). The catalyst was then filtered off and the filtrate was concentrated to give 2-[2-(4-aminophenoxy)ethyl]-4-methyl-5-phenyloxazole (11.0 g, 97.3%). Recrystallization from ethanol gave colorless needles. M.p. 106-107° C.

Elemental analysis

Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52

Found : C, 73.53; H, 6.11; N, 9.44

The above procedure was followed to give 2-[2-(4-aminophenoxy)ethyl]-5-ethyl-4-phenyloxazole in 98.7% yield. Recrystallization from ether-hexane gave colorless prisms. M.p. 89-90° C.

Elemental analysis

Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08

Found : C, 74.05; H, 6.28; N, 9.25

Reference Example 4

1) 2-[2-(4-Aminophenoxy)ethyl]-4-methyl-5-phenyloxazole (10.5 g) was dissolved in aceton (100 ml)-methanol (30 ml), and 47% aqueous HBr (24.6 g) was added to the solution, followed by dropwise addition of a solution of $NaNO_2$ (2.7 g) in water (10 ml) at 5° C. The mixture was stirred at 5° C for 15 minutes and methyl acrylate (18.4 g) was added thereto. The resulting mixture was then warmed to 38° C and, with stirring vigorously, cupurous oxide powder (1 g) was added portionwis to the mixture.

The mixtur was stirred until completion of nitrogen gas generation, then concentrated, and the residue was made basic with aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dri d ($MgSO_4$). The solvent was distilled off to giv crude 2-bromo-3-{4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]phenyl}propionate as an oil (14.3 g, 89.9%).

IR(Neat)cm^{-1}: 1740

NMR δ ppm in $CDCl_3$: 2.37(3H,s), 3.0~3.6(2H,m), 3.25(2H,t,J = 7), 3.67(3H,s), 4.2~4.5(3H,m), 6.7~7.7-(9H,m).

2) To a solution of the oily substance (14.0 g) obtained in the above procedure 1) in ethanol (150 ml) were added thiourea (2.4 g) and sodium acetate (2.6 g), and the mixture was stirred under reflux for 3 hours and then concentrated. The residue was neutralized with saturated aqueous sodium hydrogen carbonate, followed by addition of ether (50 ml)-hexane (50 ml). The mixture was stirred for 10 minutes and the resulting crystalline precipitate was collected by filtration to give 2-imino-5-{4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]benzyl}-4-thiazolidinone (6.0 g, 46.2%). Recrystallization from chloroform-methanol gave colorless prisms. M.p. 194-195°C.

Elemental analysis

Calcd. for $C_{22}H_{21}N_3O_3S$: C, 64.85; H, 5.19; N, 10.31

Found : C, 64.67; H, 5.03; N, 10.02

In the same manner as above, there was obtained 5-{4-[2-(5-ethyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-2-imino-4-thiazolidinone. The overall yield from the corresponding amino compound was 39.2%. Recrystallization from methanol gave colorless prisms. M.p. 164-165°C.

Elemental analysis

Calcd. for $C_{23}H_{23}N_3O_3S$: C, 65.54; H, 5.50; N, 9.97

Found : C, 65.32; H, 5.42; N, 9.95

Reference Example 5

A solution of 4-isobutyl-5-methyl-2-[2-(4-nitrophenoxy)ethyl]oxazole (7.8 g) in methanol (100 ml) was subjected to catalytic reduction in the presence of 5% Pd-C (wet, 2.0 g). The catalyst was then filtered off and the filtrate was concentrated to give an amino compound as an oil. The amino compound was dissolved in acetone (50 ml)-methanol (20 ml), and 47% aqueous HBr (17.9 g) was added, followed by dropwise addition of a solution of $NaNO_2$ (1.9 g) in water (6 ml) at 5°C or lower. The mixture was stirred at 5°C for 15 minutes. Methyl acrylate (15.7 g) was then added and the resulting mixture was warmed to 38°C and, with stirring vigorously, cupurous oxide powder (0.5 g) was added portionwise to the mixture. The mixture was stirred until completion of nitrogen gas generation and then concentrated. The residue was made basic with aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was distilled off to give crude methyl 2-bromo-3-[4-[2-(4-isobutyl-5-methyl-2-oxazolyl)ethoxy]phenyl]propione as an oil (9.5 g, 86.4%).

IR(Neat)cm^{-1}: 1740

NMR δ ppm in $CDCl_3$: 0.88(6H,d,J = 7), 1.8-2.1(1H,m), 2.17(3H,s), 2.2~2.4(2H,m), 3.0~3.5(2H,m), 3.12-(2H,t,J = 7), 3.68(3H,s), 4.2-4.5(1H,m), 4.28(2H,t,J = 7), 6.7-7.4(4H,m)

2) To a solution of the oily product (9.2 g) obtained in the above procedure 1) in ethanol (100 ml) were added thiourea (1.7 g) and sodium acetate (1.8 g), and the mixture was stirred under reflux for 3 hours and then concentrated. The residue was n utralized with saturated aqueous sodium hydrogen carbonat , followed by addition of ether(50 ml)-hexane (50 ml). The mixture was stirred for 10 minutes and the resulting crystalline precipitate was collected by filtration and recrystallized from ethyl acetate to give 2-imino-5-{4-[2-(4-isobutyl-5-methyl-2-oxazolyl) thoxy]b nzyl}-4-thiazolidinone (3.0 g, 35.7%) as colorless prisms. M.p. 167-168°C.

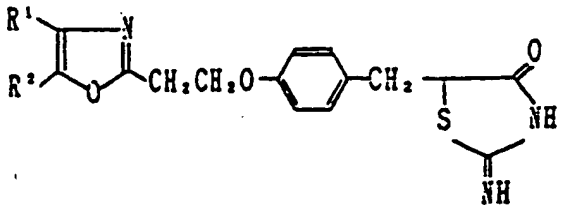
Elemental analysis

Calcd. for $C_{20}H_{25}N_3O_3S$: C, 61.99; H, 6.50; N, 10.84

Found : C, 61.96; H, 6.39; N, 10.70

In the same manner as above, there were obtained the compounds listed in Table 6. The yield is the overall yield from the corresponding starting amino compound.

Table 6



R^1	R^2	M.P. (°C)	Recrystallization solvent	Yield (%)
	CH_3	152-154	Ethyl acetate	30.1
	CH_3	178-180	Methanol	47.2

Test Example

Blood sugar and lipid lowering activities in mice

The test compound was mixed with a powder diet (CE-2, Clea Japan) at an addition level of 0.005% and the diet was given to KKA^y mice (male, 8-10 weeks old; 5 mice per group) ad libitum for 4 days, during which the mice were freely accessible to water. Blood samples were collected from the orbital venous plexus and assayed for blood sugar level by the glucose oxidase method and for plasma triglyceride (TG) level by enzymaticlly determining glycerol formed using Cleantech TG-S kit (Iatron). Both the activity levels were calculated using the formula given below. The results thus obtained are shown in Table 7. For comparison, data for a known compound of a similar structure are also given.

$$\frac{(\text{Level in untreated group}) - (\text{Level in treated group})}{(\text{Level in untreated group})} \times 100$$

Table 7

	Blood sugar (%) lowering activity	TG lowering activity (%)
1	18*	7
2	53****	43***
3	54****	51****
4	54****	60****
5	46****	51****
6	35**	24
7	43***	43**
control compound 1) ciglitazone	10	−13

t−Test *P<0.05, **P<0.02, ***P<0.01,

****P<0.001

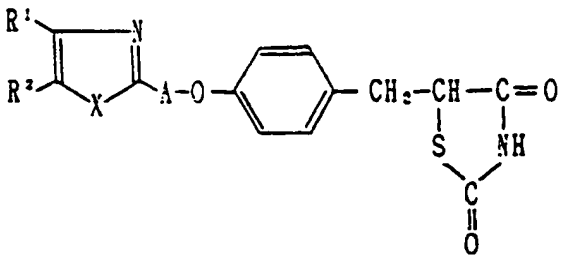
1) 5−[4−(1−Methylcyclohexylmethoxy)]

benzyl−2,4−thiazolidinedione

Claims

Claims for the following Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A thiazolidinedione derivative of the general formula:



wher in

X is an oxygen or sulfur atom,

R^1 and R^2 ach independently is

a saturated aliphatic hydrocarbon r sidue containing 1 to 8 carbon atoms,

a saturated alicyclic hydrocarbon residue containing 3 to 7 carbon atoms,

an unsaturated alicyclic hydrocarbon residue containing 5 to 7 carbon atoms,

a group resulting from bonding the above-mentioned alicyclic hydrocarbon residue to th above-mentioned aliphatic hydrocarbon residue and containing 4 to 9 carbon atoms,
a phenylalkyl group containing 7 to 9 carbon atoms,
a naphthylalkyl group containing 11 to 13 carbon atoms, phenyl or naphthyl;

i) R^1 and R^2 each being unsubstituted or substituted by one to three lower alkyl groups containing 1 to 3 carbon atoms when R^1 and R^2 each is an alicyclic hydrocarbon or contains an alicyclic hydrocarbon,
or
ii) R^1 and R^2 each being unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms when R^1 and R^2 each is phenyl or naphthyl or contains phenyl or naphthyl,
or
R^1 and R^2 are combined together to form a saturated or unsaturated divalent chain hydrocarbon residue containing 3 to 5 carbon atoms, which is unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms,
and
A is a lower alkylene group having 1 to 3 carbon atoms, or a salt thereof.

2. A compound as claimed in claim 1, wherein R^1 is a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms, a saturated alicyclic hydrocarbon residue containing 3 to 7 carbon atoms, a phenyl or a naphthyl.

3. A compound as claimed in claim 1, wherein R^2 is a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms, a phenyl or a naphthyl.

4. A compound as claimed in claim 1, wherein R^1 and R^2 jointly, together with the oxazole or thiazole ring, form a condensed ring.

5. A compound as claimed in claim 1, wherein X is an oxygen.

6. A compound as claimed in claim 1, wherein X is sulfur.

7. A compound as claimed in claim 1, wherein A is methylene.

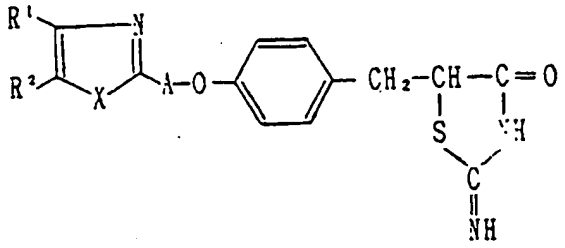
8. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(4-isobutyl-5-methyl-2-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

9. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(4-cyclohexyl-5-methyl-2-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione.

10. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

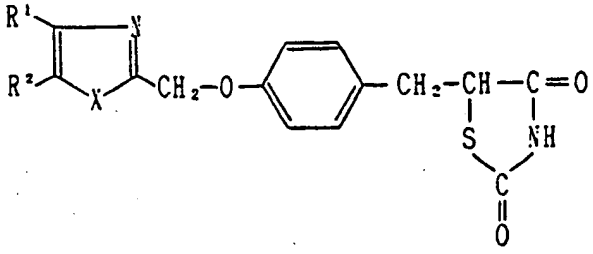
11. A pharmaceutical composition suitable for the therapy of a mammal suffering from diabetes and/or hyperlipemia which contains as the effective component a thiazolidinedione derivative as defined in claim 1, or a pharmacologically acceptable salt thereof.

12. A method of producing a thiazolidinedion derivativ as defin d in claim 1, or a salt thereof, which comprises hydrolyzing a compound of the general formula:

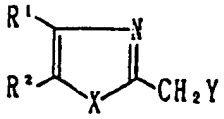


wherein the symbols are as defined in Claim 1, or a salt thereof.

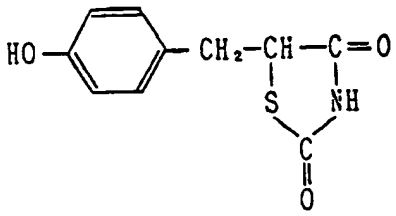
13. A method of producing a thiazolidinedione derivative of the general formula:



wherein the symbols are as defined in claim 1, or a salt thereof, which comprises reacting a compound of the general formula:

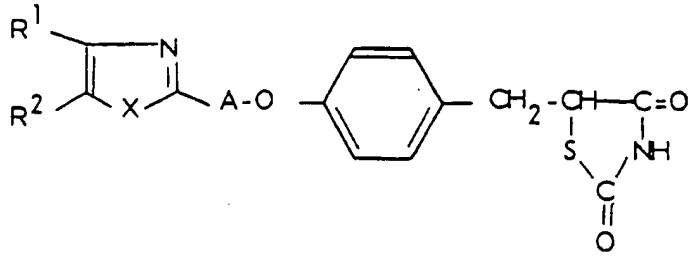


wherein Y is a halogen atom and the other symbols are as defined in Claim 1, with a compound of the formula:



Claims for the following Contracting State: AT

1. A method of producing a thiazolidinedione derivative of the general formula:



wherein

X is an oxygen or sulfur atom,

R^1 and R^2 each independently is

a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms,

a saturated alicyclic hydrocarbon residue containing 3 to 7 carbon atoms,

an unsaturated alicyclic hydrocarbon residue containing 5 to 7 carbon atoms,

a group resulting from bonding the above-mentioned alicyclic hydrocarbon residue to the above-mentioned aliphatic hydrocarbon residue and containing 4 to 9 carbon atoms,

a phenylalkyl group containing 7 to 9 carbon atoms,

a naphthylalkyl group containing 11 to 13 carbon atoms, phenyl or naphthyl;

i) R^1 and R^2 each being unsubstituted or substituted by one to three lower alkyl groups containing 1 to 3 carbon atoms when R^1 and R^2 each is an alicyclic hydrocarbon or contains an alicyclic hydrocarbon,

or

ii) R^1 and R^2 each being unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms when R^1 and R^2 each is phenyl or naphthyl or contains phenyl or naphthyl,

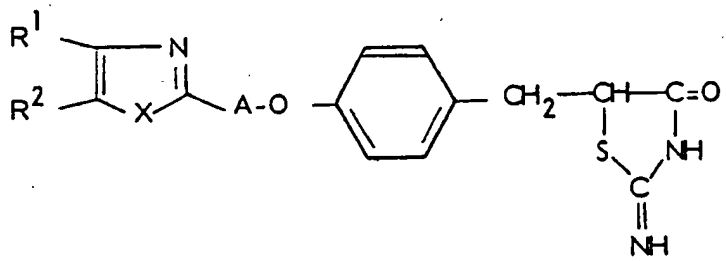
or

R^1 and R^2 are combined together to form a saturated or unsaturated divalent chain hydrocarbon residue containing 3 to 5 carbon atoms, which is unsubstituted or substituted by one to four substituents selected from halogen, hydroxy, cyano, trifluoromethyl, lower alkoxy containing 1 to 4 carbon atoms, lower alkyl containing 1 to 4 carbon atoms and lower alkylthio containing 1 to 3 carbon atoms,

and

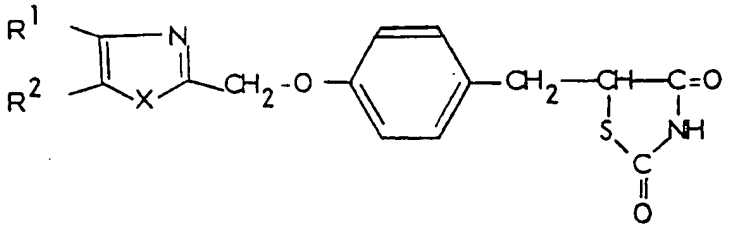
A is a lower alkylene group having 1 to 3 carbon atoms, or a salt thereof,

which comprises hydrolyzing a compound of the general formula:

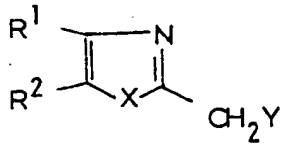


wherein the symbols are as defined above, or a salt thereof.

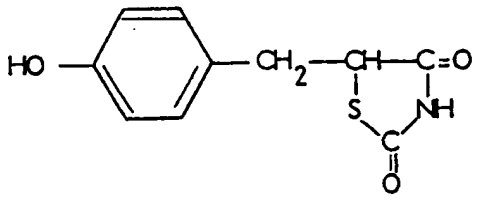
2. A method of producing a thiazolidinedione derivative of the general formula:



wherein the symbols are as defined in claim 1, or a salt thereof, which comprises reacting a compound of the general formula:



wherein Y his a halogen atom and the other symbols are as defined in Claim 1, with a compound of the formula:



3. A method as claimed in claim 1 or 2, wherein R^1 is a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms, a saturated alicyclic hydrocarbon residue containing 3 to 7 carbon atoms, a phenyl or a naphthyl.

4. A method as claimed in any of claims 1 to 3, wherein R^2 is a saturated aliphatic hydrocarbon residue containing 1 to 8 carbon atoms, a phenyl or a naphthyl.

5. A method as claimed in claim 1 or 2, wherein R^1 and R^2 jointly, together with the oxazole or thiazole ring, form a condensed ring.

6. A method as claimed in any of claims 1 to 5, wherein X is an oxygen.

7. A method as claimed in any of claims 1 to 5, wherein X is sulfur.

8. A method as claimed in any of claims 1 and 3 to 7, wherein A is methylene.

9. A method as claimed in claim 1 or 2, wherein the derivative is 5-{4-[2-(4-isobutyl-5-methyl-2-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

10. A method as claimed in claim 1 or 2, wherein the derivative is 5-{4-[2-(4-cyclohexyl-5-methyl-2-oxazolyl)ethoxy]benzyl}-2,4-thiazolidin dione.

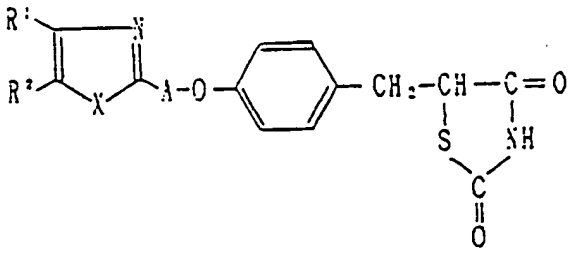
11. A method as claimed in claim 1 or 2, wherein the derivative is 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

12. A pharmaceutical composition suitable for the therapy of a mammal suffering from diabetes and/or hyperlipemia which contains as the effective component a thiazolidinedione derivative as defined in claim 1, or a pharmacologically acceptable salt thereof.

Revendications

Revendications pour les Etats contractants suivants: BE CH DE FR GB IT LI LU NL SE

1. Dérivé de thiazolidinedione répondant à la formule générale:



dans laquelle

X est un atome d'oxygène ou de soufre,

R^1 et R^2 représentent chacun, indépendamment, un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone, un radical hydrocarboné alicyclique saturé contenant de 3 à 7 atomes de carbone, un radical hydrocarboné alicyclique insaturé contenant de 5 à 7 atomes de carbone, un groupe formé par la liaison du radical hydrocarboné alicyclique mentionné ci-dessus au radical hydrocarboné aliphatique mentionné ci-dessus et contenant de 4 à 9 atomes de carbone, un groupe phénylalcoyle contenant de 7 à 9 atomes de carbone, un groupe naphtylalcoyle contenant de 11 à 13 atomes de carbone, un groupe phényle ou naphtyle;

i) R^1 et R^2 étant chacun non substitué ou substitué par 1 à 3 groupes alcoyle inférieur contenant de 1 à 3 atomes de carbone, lorsque R^1 et R^2 sont chacun un hydrocarbure alicyclique ou contiennent un hydrocarbure alicyclique, ou

ii) R^1 et R^2 étant chacun non substitué ou substitué par un à quatre substituants choisis parmi les halogènes, les groupes hydroxy, cyano, trifluorométhyle, alcoxy inférieur contenant de 1 à 4 atomes de carbone, alcoyle inférieur contenant de 1 à 4 atomes de carbone et alcoylthio inférieur contenant de 1 à 3 atomes de carbone,

lorsque R^1 et R^2 sont chacun un groupe phényle ou naphtyle ou contiennent un groupe phényle ou naphtyle, ou

R^1 et R^2 sont unis ensemble pour former le radical hydrocarboné d'une chaîne divalente saturée ou insaturée contenant de 3 à 5 atomes de carbone, qui est non substitué ou substitué par un à quatre substituants choisis parmi les halogènes, les groupes hydroxy, cyano, trifluorométhyle, alcoxy inférieur contenant de 1 à 4 atomes de carbone, alcoyle inférieur contenant de 1 à 4 atomes de carbone et alcoylthio inférieur contenant de 1 à 3 atomes de carbone, et

A est un groupe alcoylène inférieur contenant de 1 à 3 atomes de carbone

ou un sel de celui-ci.

2. Composé selon la revendication 1, dans lequel R^1 est un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone, un radical hydrocarboné alicyclique saturé contenant de 3 à 7 atomes de carbone ou un groupe phényle ou naphtyle.

3. Composé selon la revendication 1, dans lequel R^2 est un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone ou un groupe phényle ou naphtyle.

4. Composé selon la revendication 1, dans lequel R^1 et R^2 ensemble avec le cycle oxazole ou thiazole form nt un cycle condensé.

5. Composé s lon la rev ndication 1, dans lequel X est l'oxygèn .

6. Composé selon la revendication 1, dans lequel X est le soufre.

7. Composé selon la revendication 1, dans lequel A est le méthylène.

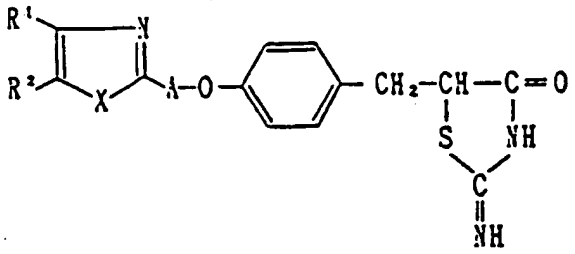
8. Composé selon la revendication 1, qui est la 5-{4-[2-(4-isobutyl-5-méthyl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

9. Composé selon la revendication 1, qui est la 5-{4-[2-(4-cyclohexyl-5-méthyl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

10. Composé selon la revendication 1, qui est la 5-{4-[2-(5-méthyl-4-phényl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

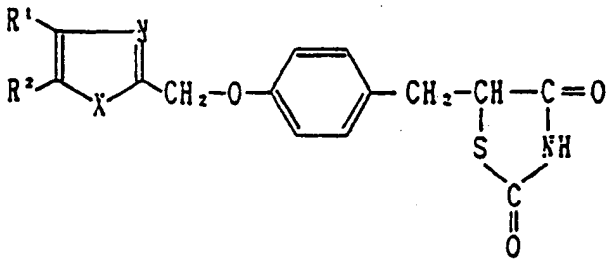
11. Composition pharmaceutique utilisable pour le traitement d'un mammifère atteint de diabète et/ou d'hyperlipémie, qui contient comme composé actif un dérivé de thiazolidinedione tel que défini à la revendication 1 ou un sel pharmacologiquement acceptable de celui-ci.

12. Procédé de préparation d'un dérivé de thiazolidinedione tel que défini à la revendication 1 ou d'un sel de celui-ci, qui comprend l'hydrolyse d'un composé répondant à la formule générale:

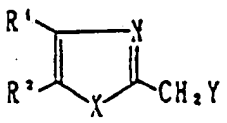


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci.

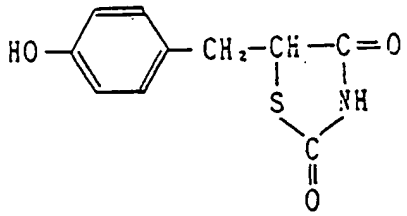
13. Procédé de préparation d'un dérivé de thiazolidinedione répondant à la formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:

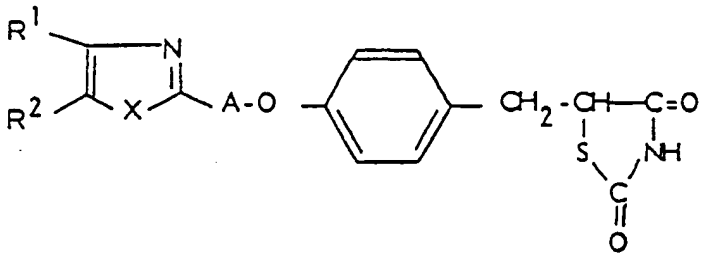


dans laquelle Y est un atome d'halogène et les autres symbol s sont tels que défini à la revendication 1, avec un composé de formule:



Revendications pour l'Etat contractant suivant: AT

1. Procédé de préparation d'un dérivé de thiazolidinedione répondant à la formule générale:



dans laquelle

X est un atome d'oxygène ou de soufre,

R^1 et R^2 représentent chacun, indépendamment, un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone, un radical hydrocarboné alicyclique saturé contenant de 3 à 7 atomes de carbone, un radical hydrocarboné alicyclique insaturé contenant de 5 à 7 atomes de carbone, un groupe formé par la liaison du radical hydrocarboné alicyclique mentionné ci-dessus au radical hydrocarboné aliphatique mentionné ci-dessus et contenant de 4 à 9 atomes de carbone, un groupe phénylalcoyle contenant de 7 à 9 atomes de carbone, un groupe naphtylalcoyle contenant de 11 à 13 atomes de carbone, un groupe phényle ou naphtyle;

i) R^1 et R^2 étant chacun non substitué ou substitué par 1 à 3 groupes alcoyle inférieur contenant de 1 à 3 atomes de carbone, lorsque R^1 et R^2 sont chacun un hydrocarbure alicyclique ou contiennent un hydrocarbure alicyclique, ou

ii) R^1 et R^2 étant chacun non substitué ou substitué par un à quatre substituants choisis parmi les halogènes, les groupes hydroxy, cyano, trifluorométhyle, alcoxy inférieur contenant de 1 à 4 atomes de carbone, alcoyle inférieur contenant de 1 à 4 atomes de carbone et alcoylthio inférieur contenant de 1 à 3 atomes de carbone,

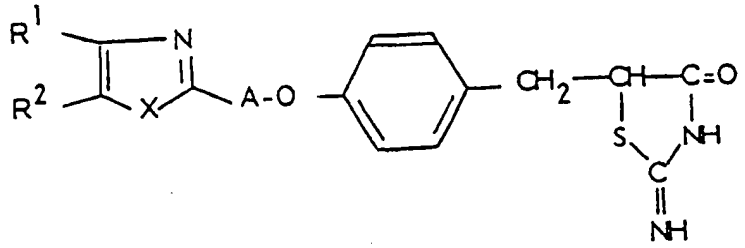
lorsque R^1 et R^2 sont chacun un groupe phényle ou naphtyle ou contiennent un groupe phényle ou naphtyle, ou

R^1 et R^2 sont unis ensemble pour former le radical hydrocarboné d'une chaîne divalente saturée ou insaturée contenant de 3 à 5 atomes de carbone, qui est non substitué ou substitué par un à quatre substituants choisis parmi les halogènes, les groupes hydroxy, cyano, trifluorométhyle, alcoxy inférieur contenant de 1 à 4 atomes de carbone, alcoyle inférieur contenant de 1 à 4 atomes de carbone et alcoylthio inférieur contenant de 1 à 3 atomes de carbone, et

A est un groupe alcoylène inférieur contenant de 1 à 3 atomes de carbone

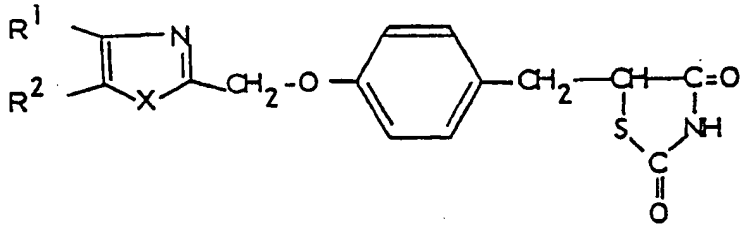
ou d'un sel de celui-ci,

qui comprend l'hydrolyse d'un composé de formule générale:

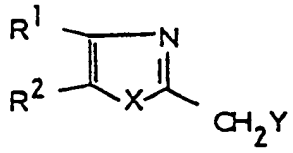


dans laquelle les symboles sont tels que défini ci-dessus, ou d'un sel de celui-ci.

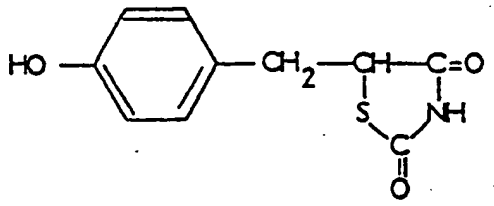
2. Procédé de préparation d'un dérivé de thiazolidinedione répondant à la formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:



dans laquelle Y est un atome d'halogène et les autres symboles sont tels que défini à la revendication 1, avec un composé de formule:



3. Procédé selon la revendication 1 ou 2, dans lequel R^1 est un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone, un radical hydrocarboné alicyclique saturé contenant de 3 à 7 atomes de carbone ou un groupe phényl ou naphtyl .

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel R^2 est un radical hydrocarboné aliphatique saturé contenant de 1 à 8 atomes de carbone ou un groupe phényle ou naphtyle.

5. Procédé selon la revendication 1 ou 2, dans lequel R^1 et R^2 ensemble avec le cycle oxazole ou thiazole forment un cycle condensé.

6. Procédé s lon l'une quelconque des revendications 1 à 5, dans lequel X est l'oxygène.

7. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel X est le soufre.

8. Procédé selon l'une quelconque des revendications 1 et 3 à 7, dans lequel A est le méthylène.

9. Procédé selon la revendication 1 ou 2, dans lequel le dérivé est la 5-{4-[2-(4-isobutyl-5-méthyl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

10. Procédé selon la revendication 1 ou 2, dans lequel le dérivé est la 5-{4-[2-(4-cyclohexyl-5-méthyl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

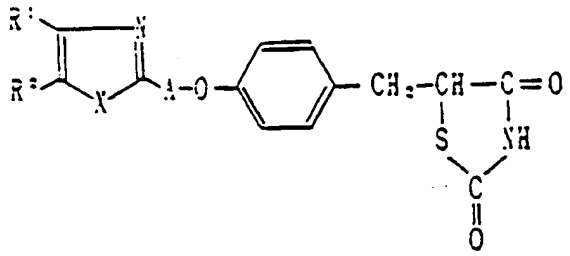
11. Procédé selon la revendication 1 ou 2, dans lequel le dérivé est la 5-{4-[2-(5-méthyl-4-phényl-2-oxazolyl)éthoxy]benzyl}-2,4-thiazolidinedione.

12. Composition pharmaceutique utilisable pour le traitement d'un mammifère atteint de diabète et/ou d'hyperlipémie, qui contient comme composé actif un dérivé de thiazolidinedione tel que défini à la revendication 1 ou un sel pharmacologiquement acceptable de celui-ci.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Thiazolidindionderivat der allgemeinen Formel



worin X ein Sauerstoff- oder Schwefelatom ist, R^1 und R^2 jeweils unabhängig ein gesättigter aliphatischer Kohlenwasserstoffrest mit 1 bis 8 C-Atomen, ein gesättigter alicyclischer Kohlenwasserstoffrest mit 3 bis 7 C-Atomen, ein ungesättigter alicyclischer Kohlenwasserstoffrest mit 5 bis 7 C-Atomen, eine Gruppe, die durch Bindung des vorstehend angeführten alicyclischen Kohlenwasserstoffrestes an den vorstehend angeführten aliphatischen Kohlenwasserstoffrest entsteht und 4 - 9 C-Atome enthält, eine Phenylalkylgruppe mit 7 - 9 C-Atomen, eine Naphthylalkylgruppe mit 11 - 13 C-Atomen, Phenyl oder Naphtyl ist;

i) R^1 und R^2 jeweils gegebenenfalls durch 1 - 3 Niederalkylgruppen mit 1 - 3 C-Atomen substituiert sind, wenn R^1 und R^2 jeweils einen alicyclischen Kohlenwasserstoff darstellen oder einen solchen enthalten, oder

ii) R^1 und R^2 jeweils gegebenenfalls durch 1 - 4 Substituenten substituiert sind, die aus Halogen, Hydroxy, Cyano, Trifluormethyl, Niederalkoxy mit 1 - 4 C-Atomen, Niederalkyl mit 1 - 4 C-Atomen und Niederalkylthio mit 1 - 3 C-Atomen gewählt sind, wenn R^1 und R^2 jeweils Phenyl oder Naphthyl darstellen oder Phenyl oder Naphthyl enthalten, oder

R^1 und R^2 miteinander kombiniert werden, um einen gesättigten oder ungesättigten zweiwertigen kettenförmigen Kohlenwasserstoffrest mit 3 - 5 C-Atomen zu bilden, der gegebenenfalls durch 1 - 4 Substituenten substituiert ist, die aus Halogen, Hydroxy, Cyano, Trifluormethyl, Niederalkoxy mit 1 - 4 C-Atomen, Niederalkyl mit 1 - 4 C-Atomen und Niederalkylthio mit 1 - 3 C-Atomen gewählt sind und

A eine niedere Alkylengruppe mit 1 - 3 C-Atomen darstellt, oder ein Salz desselben.

2. Verbindung nach Anspruch 1, worin R^1 einen gesättigten aliphatischen Kohlenwasserstoffrest mit 1 - 8 C-Atomen, einen g sättigten alicyclischen Kohlenwasserstoffrest mit 3 - 7 C-Atomen, ein Phenyl oder ein Naphthyl darstellt.

3. Verbindung nach Anspruch 1, worin R^2 ein gesättigter aliphatischer Kohlenwasserstoffrest mit 1 - 8 C-Atomen, ein Phenyl oder ein Naphthyl ist.

4. Verbindung nach Anspruch 1, worin R^1 und R^2 gemeinsam zusammen mit dem Oxazol- oder Thiazolring einen kondensierten Ring bilden.

5. Verbindung nach Anspruch 1, worin X Sauerstoff ist.

6. Verbindung nach Anspruch 1, worin X für Schwefel steht.

7. Verbindung nach Anspruch 1, worin A Methylen darstellt.

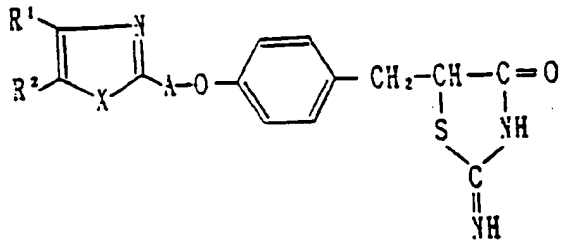
8. Verbindung nach Anspruch 1, worin die Verbindung 5-(4-|2-(4-Isobutyl-5-methyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

9. Verbindung nach Anspruch 1, worin die Verbindung 5-(4-|2-(4-Cyclohexyl-5-methyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

10. Verbindung nach Anspruch 1, worin die Verbindung 5-(4-|2-(5-Methyl-4-phenyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

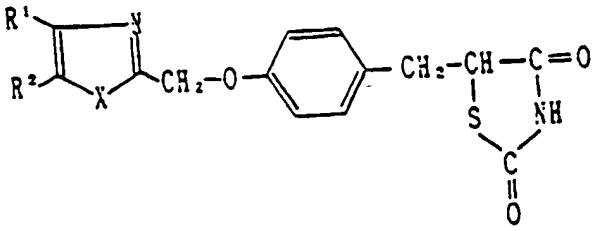
11. Pharmazeutische Zusammensetzung, die für die Therapie eines Säugetieres geeignet ist, das an Diabetes und/oder Hyperlipämie leidet, die als wirksamen Bestandteil ein wie in Anspruch 1 definiertes Thiazolidindionderivat enthält, oder ein pharmakologisch verträgliches Salz desselben.

12. Verfahren zur Herstellung eines Thiazolidindionderivates nach Anspruch 1 oder eines Salzes desselben, das das Hydrosysieren einer Verbindung der allgemeinen Formel



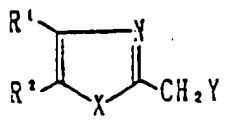
umfaßt, worin die Symbole die in Anspruch 1 angeführte Bedeutung besitzen, oder eines Salzes derselben.

13. Verfahen zur Herstellung eines Thiazolidindionderivates der allgemeinen Formel

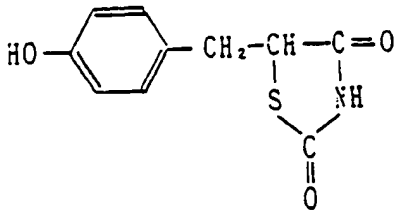


worin die Symbole di in Anspruch 1 angeführte Bedeutung besitzen, oder eines Salzes desselben, das

die Umsetzung ein r Verbindung der allgemeinen Formel



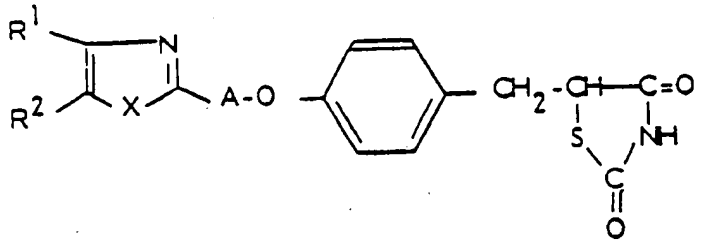
worin Y ein Halogenatom darstellt und die anderen Symbole die in Anspruch 1 angeführte Bedeutung besitzen, mit einer Verbindung der Formel



umfaßt.

Patentansprüche für folgenden Vertragsstaat: AT

1. Verfahren zur Herstellung eines Thiazolidindionderivates der allgemeinen Formel



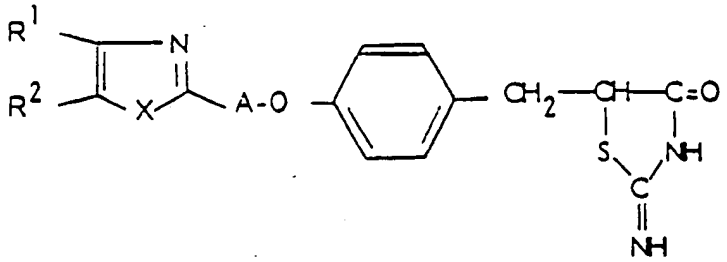
worin X ein Sauerstoff-oder Schwefelatom ist, R^1 und R^2 jeweils unabhängig ein gesättigter aliphatischer Kohlenwasserstoffrest mit 1 bis 8 C-Atomen, ein gesättigter alicyclischer Kohlenwasserstoffrest mit 3 bis 7 C-Atomen, ein ungesättigter alicyclischer Kohlenwasserstoffrest mit 5 bis 7 C-Atomen, eine Gruppe, die durch Bindung des vorstehend angeführten alicyclischen Kohlenwasserstoffrestes an den vorstehend angeführten aliphatischen Kohlenwasserstoffrest entsteht und 4 - 9 C-Atome enthält, eine Phenylalkylgruppe mit 7 -9 C-Atomen, eine Naphthylalkylgruppe mit 11 -13 C-Atomen, Phenyl oder Naphthyl ist;

i) R^1 und R^2 jeweils gegebenenfalls durch 1 - 3 Niederalkylgruppen mit 1 - 3 C-Atomen substituiert sind, wenn R^1 und R^2 jeweils einen alicyclischen Kohlenwasserstoff darstellen oder einen solchen enthalten, oder

ii) R^1 und R^2 jeweils gegebenenfalls durch 1 - 4 Substituenten substituiert sind, die aus Halogen, Hydroxy, Cyano, Trifluormethyl, Niederalkoxy mit 1 - 4 C-Atomen, Niederalkyl mit 1 - 4 C-Atomen und Niederalkylthio mit 1 - 3 C-Atomen gewählt sind, wenn R^1 und R^2 jeweils Phenyl oder Naphthyl darstellen oder Phenyl oder Naphthyl enthalten, oder

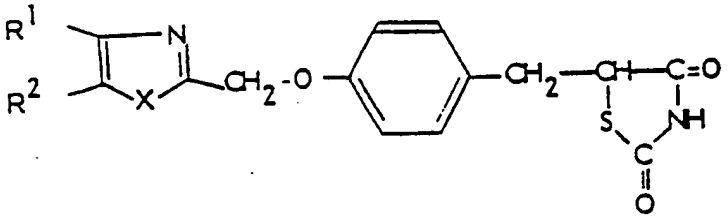
R^1 und R^2 miteinander kombiniert w rden, um einen gesättigten oder ungesättigten zweiwertigen k ttenförmig n Kohlenwasserstoffrest mit 3 - 5 C-Atomen zu bilden, der geg benenfalls durch 1 - 4 Substituenten substitui rt ist, die aus Halogen, Hydroxy, Cyano, Trifluormethyl, Niederalkoxy mit 1 - 4 C-Atomen, Niederalkyl mit 1 - 4 C-Atomen und Nied ralkylthio mit 1 - 3 C-Atomen gewählt sind und

A eine niedere Alkylengruppe mit 1 - 3 C-Atomen darstellt, oder eines Salzes desselben, das das Hydrolysi r n einer Verbindung der allgemeinen Form l

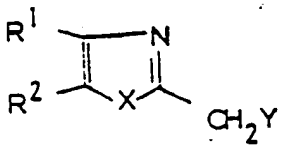


umfaßt, worin die Symbole die vorstehend angeführte Bedeutung besitzen, oder eines Salzes derselben.

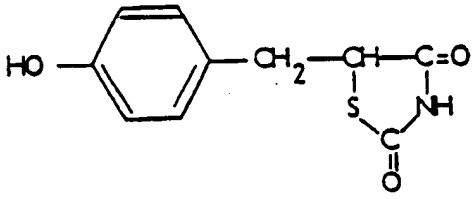
2. Verfahren zur Herstellung eines Thiazolidindionderivates der allgemeinen Formel



worin die Symbole die in Anspruch 1 angeführte Bedeutung besitzen, oder eines Salzes desselben, welches das Umsetzen einer Verbindung der allgemeinen Formel



worin Y ein Halogenatom darstellt und die anderen Symbole die in Anspruch 1 angeführte Bedeutung besitzen, mit einer Verbindung der Formel



umfaßt.

3. Verfahren nach Anspruch 1 oder 2, worin R^1 einen gesättigten aliphatischen Kohlenwasserstoffrest mit 1 - 8 C-Atomen, einen gesättigten alicyclischen Kohlenwasserstoffrest mit 3 - 7 C-Atomen, ein Phenyl oder ein Naphthyl darstellt.

4. Verfahren nach einem der Ansprüche 1 bis 3, worin R^2 ein gesättigter aliphatischer Kohlenwasserstoff-

rest mit 1 - 8 C-Atomen, ein Phenyl oder ein Naphthyl ist.

5. Verfahren nach Anspruch 1 oder 2, worin R^1 und R^2 gemeinsam zusammen mit dem Oxazol- oder Thiazolring einen kondensierten Ring bilden.

6. Verfahren nach einem der Ansprüche 1 bis 5, worin X Sauerstoff ist.

7. Verfahren nach einem der Ansprüche 1 bis 5, worin X für Schwefel steht.

8. Verfahren nach einem der Ansprüche 1 und 3 bis 7, worin A Methylen darstellt.

9. Verfahren nach Anspruch 1 oder 2, worin das Derivat 5-(4-|2-(4-Isobutyl-5-methyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

10. Verfahren nach Anspruch 1 oder 2, worin das Derivat 5-(4-|2-(4-Cyclohexyl-5-methyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

11. Verfahren nach Anspruch 1 oder 2, worin das Derivat 5-(4-|2-(5-Methyl-4-phenyl-2-oxazolyl)-äthoxy|benzyl)-2,4-thiazolidindion ist.

12. Pharmazeutische Zusammensetzung, die für die Therapie eines Säugetieres geeignet ist, das an Diabetes und/oder Hyperlipämie leidet, die als wirksamen Bestandteil ein wie in Anspruch 1 definiertes Thiazolidindionderivat enthält, oder ein pharmakologisch verträgliches Salz desselben.